

Taking the "Idio" Out of Idiopathic Pulmonary Fibrosis

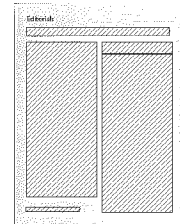
A Call to Arms

The Merriam-Webster dictionary lists two uses for "idiopathic" (1). The primary definition is one we have embraced in medicine as part of the litany (e.g., hereditary, infectious, etc.) of potential causes for every ailment: "arising spontaneously or from an obscure or unknown cause." This use has been embarrassingly accurate for the pathologic findings in lung parenchyma that we call idiopathic pulmonary fibrosis (IPF) (2, 3). Of note, we don't know the causes of other pathologic patterns of pulmonary fibrosis (e.g., desquamative interstitial pneumonia [DIP] or non-specific interstitial pneumonia [NSIP]) either. IPF has been "idiopathic" at multiple levels. We don't know the initiating factors or injuries, and we don't know why the fibrosis is progressive and dysregulated.

These are exciting times for those who study IPF. One recent study identified mutations in the genes for hTERT and hTR, which regulate telomerase reverse transcriptase and telomerase RNA in families with IPF (4). These mutations predispose to short telomeres, which are associated with DNA damage and premature cell death. The hypothesis is that short telomeres predispose to alveolar cell death and fibrosis occurs in response to rapid turnover of epithelial lining cells. Familial IPF is thus a limited form of the full dyskeratosis congenital syndrome in patients with lung disease only (5). This new information adds to the list of genetic defects previously observed in IPF (6, 7). A second recent study defined the loss of protective caveolin 1 in fibroblasts of patients with IPF, thus permitting unchecked effects of transforming growth factor (TGF)- β (8). Both studies are major advances in IPF research; time will determine how common these defects may be. The results of each study imply different, and perhaps individualized, approaches to therapy.

Mora and colleagues provide us with another insight into the pathogenesis of IPF (9). Their study, in this issue of the *Journal* (pp. 1139–1150), extends the story they have helped develop related to possible pathogenic roles of human herpesvirus (HHV) and Epstein–Barr virus (EBV) in IPF lung tissue (10–12). IFN- $\gamma^{-/-}$ mice infected with the murine γ -herpesvirus murine herpes virus 68 (MHV68) develop progressive lung fibrosis. The virus is pleiotropic and infects multiple different cells in the lung. The essence of these studies is that viral reactivation is essential for progression of pulmonary fibrosis; antiviral treatment can prevent progression even if initiated after establishment of fibrosis, resulting in prolonged survival. Interestingly, although the mice are inbred, 10% of treated mice still progress to fibrosis, which, if not due to different viral loads, suggests that if herpesviruses do initiate or are cofactors for human IPF, there likely will be variable responses to antiviral therapy.

Like all good studies, that of Mora and colleagues is most important for the questions it raises. Can and do viruses set in motion the processes that result in pulmonary fibrosis? In mice, genetically altered toward Th2 skewing and impaired natural antiviral defense by deletion of the IFN- γ gene, the answer most certainly is yes. Does this prove that similar viruses in human IPF tissue are a cause of IPF? No. The model is somewhat artificial (like bleomycin) in that MHV68 bears only familial resemblance to human herpesviruses and there is no present evidence that viruses of this class reactivate and replicate with



fibrotic consequences in humans. However, the response to anti-viral therapy in this study, and a possible role for MHV68 in bleomycin-induced fibrosis, as well as the therapeutic triumphs in peptic ulcer disease and Whipple's disease should open our eyes to an active pursuit for nonhuman DNA species in **IPF** lung specimens as potential contributing factors (13).

Does this study prove that lung fibrosis is a Th2-skewed phenomena? No, not really. The study in which this hypothesis was generated is in mice, a species prone to skewing, and not in humans. There is no evidence that there is an absence of IFN- γ in human IPF and adding more has been disappointing in preventing progression of disease. However, control of virus replication in animals skewed to Th2 inflammation does halt progression of fibrosis and improve survival. Mora and coworkers (9) are ideally positioned to determine if MHV68 induces epigenetic changes in hTERT, hTR, or caveolin 1 expression, and could help reconcile whether these abnormalities are part of the final common pathway for "idiopathic" pulmonary fibrosis. Is there likely to be a unifying theme here? I suspect not. IPF is more complex. The pathologic pattern we observe in IPF could be a picture that represents the end result of responses. Moreover, herpes and EBV viruses are more likely to induce cellular changes consistent with progression of the cell cycle out of G1 and proliferation rather than shortened cell survival seen in hTERT or hTR mutations.

Regardless of whether these studies and others will identify unifying or multiple independent common pathways that lead to fibrosis of the lung from multiple initiating factors and cofactors, we should not forget the second definition of idiopathic: "peculiar to the individual" (1). IPF is a pathologic pattern. We need to approach this pattern as oncologists now approach many cancers, by developing individual gene profiles that will help predict prognosis, response to therapy, and, it is hoped, etiology. IPF is a terrible disease. We are just beginning to understand why our therapeutic approaches over the past decades don't work.

The call to arms is clear:

1. We need to support exhaustive searches for nonhuman DNA in all forms of pulmonary fibrosis, not just IPF. If any single case of IPF can be attributed to a treatable infectious agent, then we will have succeeded in this endeavor.
2. We need to initiate high-density single-nucleotide polymorphism and haplotype mapping in sporadic (nonfamilial) cases of pulmonary fibrosis to complement the family-based genetic profiles.
3. We need to support genomic (and eventually proteomic) studies of lung tissue to identify candidate genes and to develop gene profiles that predict prognosis, response to therapy, and initiating factors suitable for individual cases. Ideally, we would search for a tissue that reflects the response in lung without resorting to lung biopsy.
4. It is time to stop ignoring all "other" idiopathic forms of fibrosis in the lung.

Conflict of Interest Statement: D.M.C. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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References

1. Merriam-Webster online dictionary [Internet]. Springfield, MA: Merriam-Webster; c2005. Available from: www.webster.com.
2. American Thoracic Society; European Respiratory Society. American Thoracic Society/European Respiratory Society international multidisciplinary consensus classification of the idiopathic interstitial pneumonias. *Am J Respir Crit Care Med* 2002;165:277-304.
3. American Thoracic Society; European Respiratory Society. Idiopathic pulmonary fibrosis: diagnosis and treatment: international consensus statement. *Am J Respir Crit Care Med* 2000;161:646-664.
4. Armanios MY, Chen JJ, Cogan JD, Alder JK, Ingersoll RG, Markin C, Lawson WE, Xie M, Vulto I, Phillips JA III, et al. Telomerase mutations in families with idiopathic pulmonary fibrosis. *N Engl J Med* 2007;356:1317-1326.
5. Vulliamy TJ, Marrone A, Knight SW, Walne A, Mason PJ, Dokal I. Mutations in dyskeratosis congenita: their impact on telomere length and the diversity of clinical presentation. *Blood* 2006;107:2680-2685.
6. Grutters JC, du Bois RM. Genetics of fibrosing lung diseases. *Eur Respir J* 2005;25:915-927.
7. Thomas AQ, Lane K, Phillips J III, Prince M, Markin C, Speer M, Schwartz DA, Gaddipati R, Marney A, Johnson J, et al. Heterozygosity for a surfactant protein C gene mutation associated with usual interstitial pneumonitis and cellular nonspecific interstitial pneumonitis in one kindred. *Am J Respir Crit Care Med* 2002;165:1322-1328.
8. Wang XM, Zhang Y, Kim HP, Zhou Z, Feghali-Bostwick CA, Liu F, Ifedigbo E, Xu X, Oury TD, Kaminski N, et al. Caveolin-1: a critical regulator of lung fibrosis in idiopathic pulmonary fibrosis. *J Exp Med* 2006;203:2895-2906.
9. Mora AL, Torres-González E, Rojas M, Xu J, Ritzenthaler J, Speck SH, Roman J, Brigham K, Stecenko A. Control of virus reactivation arrests pulmonary herpesvirus-induced fibrosis in IFN- γ receptor-deficient mice. *Am J Respir Crit Care Med* 2007;175:1139-1150.
10. Stewart JP, Egan JJ, Ross AJ, Kelly BG, Lok SS, Hasleton PS, Woodcock AA. The detection of Epstein-Barr virus DNA in lung tissue from patients with idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 1999;159:1336-1341.
11. Mora AL, Woods CR, Garcia A, Xu J, Rojas M, Speck SH, Roman J, Brigham KL, Stecenko AA. Lung infection with gamma-herpesvirus induces progressive pulmonary fibrosis in Th2-biased mice. *Am J Physiol Lung Cell Mol Physiol* 2005;289:L711-L721.
12. Mora AL, Torres-Gonzalez E, Rojas M, Corredor C, Ritzenthaler J, Xu J, Roman J, Brigham K, Stecenko A. Activation of alveolar macrophages via the alternative pathway in herpesvirus-induced lung fibrosis. *Am J Respir Cell Mol Biol* 2006;35:466-473.
13. Lok SS, Haider Y, Howell D, Stewart JP, Hasleton PS, Egan JJ. Murine gammaherpes virus as a cofactor in the development of pulmonary fibrosis in bleomycin resistant mice. *Eur Respir J* 2002;20:1228-1232.

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